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## Abstract

**Purpose:** Achieving rapid protection against hepatitis B (HBV) is critical for patients with chronic renal failure (CRF). HEPLISAV™ (HBsAg-ISS) is an investigational vaccine containing hepatitis B surface antigen (HBsAg) and 1018 ISS, a Toll-like Receptor 9 agonist adjuvant. **Methods:** This was a single-blind, randomized study of 41 subjects, 40–70 years of age, with progressive loss of renal function (glomerular filtration rate [GFR] ≤ 45 mL/min/1.73m<sup>2</sup>). Subjects were randomized 1:1 to receive HBsAg-ISS either single dose or double dose, at 0, 4 and 24 weeks. Anti-HBsAg concentrations were measured at weeks 4, 12, 24, 28 and 50. Immunogenicity endpoints included seroprotection rate (SPR) and serum geometric mean concentrations (GMC). Safety of HBsAg-ISS was assessed, including local and systemic reactivity and adverse events.

**Results:** A total of 21 subjects received the single dose and 20 subjects received the double dose. Fifteen subjects were on dialysis. Forty of the 41 randomized subjects (97.6%) received the first 2 injections of study drug. Only 2 subjects (1 at each dose level) received the third injection due to premature discontinuation of the study because of an FDA-imposed clinical hold that was subsequently removed. The SPR for the combined HBsAg-ISS groups was 10% (4/40) after one dose at week 4, 58% (23/40) after 2 doses at week 12, and 100% (11/11) after 2 doses at week 24. GMC was 3.2, 20.4 and 258.7 mIU/mL at week 4, 12 and 24, respectively. No significant differences were observed in subjects pre-dialysis or on dialysis. The most frequently reported local and systemic reactogenicity events were pain at the injection site and fatigue. **Conclusion:** HBsAg-ISS was immunogenic and well-tolerated, and preliminary results suggest the potential of rapid protection against HBV in patients with chronic renal failure.

## Objectives

- to evaluate the safety and tolerability of HBsAg-ISS in CRF patients
- to evaluate the seroprotection rates (defined as antibody to HBsAg anti-HBsAg) ≥10 mIU/mL of HBsAg-ISS at 4 weeks after 3 immunizations
- to evaluate the immune response (% anti-HBsAg ≥ 10 and ≥ 100 mIU/mL) and geometric mean anti-HBsAg concentrations (GMC) at week 4, 12, 24, 28 and 50

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## Methods

**Design:** Single-blind, randomized, multi-center study  
**Subjects:** Patients with CRF (GFR ≤ 45 mL/min/1.73m<sup>2</sup>), 40 - 70 years of age with negative history of hepatitis B infection or vaccination  
**Vaccine, Dosage, and Schedule**  
 • HBsAg-ISS (single dose or double dose) at week 0, 4, and 24  
 • Randomization 1:1 (single dose: double dose)  
**Clinical Safety Monitoring:**  
 • medical history each visit  
 • immediate post-vaccination events for 30 minutes  
 • local injection-site and systemic reactions by daily diary for 7 days post each dose; telephone contact at 72 hours post each dose  
 • concomitant medications, medical interventions, and (serious) adverse events throughout the study  
**Immunological Monitoring:** anti-HBsAg at baseline and weeks 4, 12, 24, 28 and 50

## Results

- 41 subjects enrolled at 3 clinical sites in Canada (21 in single-dose group; 20 in double-dose group)
- Demographics: mean age 57.5 years (SD 8.7) and 66.7% male in single-dose group; mean age 60.3 years (SD 8.9) and 70% male in double-dose group
- 15 patients were on dialysis; 26 pre-dialysis patients
- 40 (97.6%) of subjects received 2 of 3 planned immunizations; only 2 subjects received all 3 immunizations.
- Due to premature discontinuation of the study, no statistical conclusions can be obtained and results are descriptive only.

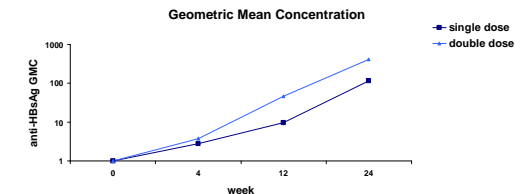
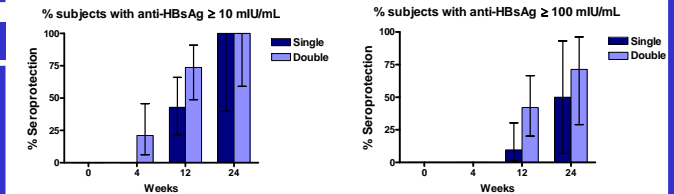
## Safety

|   | Single Dose<br>N = 21 | Double Dose<br>N = 20 |
|---|-----------------------|-----------------------|
| <b>% Subjects with any local reaction</b>   |                       |                       |
| Dose 1                                      | 14.3%                 | 10.0%                 |
| Dose 2                                      | 5.0%                  | 21.1%                 |
| <b>% Subjects with any general reaction</b> |                       |                       |
| Dose 1                                      | 9.5%                  | 30.0%                 |
| Dose 2                                      | 5.0%                  | 26.3%                 |

- Majority of local and systemic adverse events (AE) observed were mild to moderate in severity and were self-limited.
- Pain at the injection site and fatigue were the most common local and systemic reactions reported.
- Single dose was better tolerated than double dose, with 3-5 fold fewer general reactions.

## Immunogenicity

- SPR (defined as anti-HBsAg ≥ 10 mIU/mL) for the single-dose was 43% (95% CI, 22% - 66%) and for the double-dose 74% (49% - 91%) at 8 weeks after the 2<sup>nd</sup> immunization. SPR was 100% for both groups 20 weeks after the 2<sup>nd</sup> immunization (lower limit of 95% CI, 40% for single-dose and 59% for the double-dose).
- Percentage of subjects who achieved anti-HBsAg titers ≥ 100 mIU/mL in the single- and double-dose groups was 50% (95% CI, 7% - 93%) and 71% (29% - 96%) at 20 weeks after the 2<sup>nd</sup> immunization, respectively.
- GMC for the single- and double-dose groups at 20 weeks after only 2 immunizations was 115.5 and 410.2 mIU/mL, respectively.
- No differences were observed in subjects pre-dialysis or on dialysis.



## Conclusions

- This study suggests that single-dose HBsAg-ISS is immunogenic and well-tolerated in renal pre-dialysis and dialysis patients.
- Preliminary results suggest the potential of rapid protection against HBV in patients with chronic renal failure.
- A large phase-3 RCT is currently ongoing in CRF patients (both pre-dialysis and on dialysis) comparing 3 single doses of HBsAg-ISS vs 8 doses of Engerix-B.